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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/418,221	10/14/1999	NAGESH K. MAHANTHAPPA	ONV-043.01(1	8622

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ROPES & GRAY
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
BRANNOCK, MICHAEL T	
ART UNIT	**PAPER NUMBER**
1646	23

DATE MAILED: 01/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

Office Action Summary	Application No. 09/418,221	Applicant(s) Mahanthappa et al.
	Examiner Michael Brannock	Art Unit 1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 22, 2002* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 3-6, 18-23, 25-28, and 39-49* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 3-6, 18-23, 25-28, and 39-49* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application: Claims and Amendments

1. Applicant is notified that the amendments put forth in Paper 20, 10/22/02, have been entered in full.

2. Claims 1, 3-6, 18-23, 25-28, and 39-49 are pending.

Withdrawn Rejections:

3. Applicant is notified that any outstanding rejection or objection, that is not expressly maintained in this Office Action, has been withdrawn.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 39-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

New claims 39-43 require a "bioactive fragment" of a hedgehog polypeptide. The term "bioactive" is a relative term and the specification has not defined the term such that the artisan would unambiguously know whether a given fragment was encompassed by the claims. Thus, the metes and bounds of the claims cannot be adequately determined.

6. Claims 1, 3-6, 18-23, 25-28, and 31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating cerebral ischemia, comprising the administration of a mammalian sonic hedgehog polypeptide of SEQ ID NO: 12 or 15, does not reasonably provide enablement for the treatment, prevention, or protection for other neuropathies, nor for the treatment of any neuropathy comprising the administration of polypeptide other than a mammalian sonic hedgehog polypeptide or an N-terminal auto-proteolytic fragment thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims. It is noted that the previous office Action contained two obvious clerical errors. Claim 6 was inadvertently left out of the rejection and SEQ ID NO: 15 was inadvertently referred to as SEQ ID NO: 14. These errors are obvious and do not appear to have had any impact on Applicant's response to the previous Office action.

As set forth previously, the specification presents the results obtained using a mouse model of stroke, comprising the administration of a mammalian sonic hedgehog, presumably that of the murine SEQ ID NO: 12, although it does not appear that the specification actually teaches which sonic hedgehog is used. The claims claim methods using an essentially limitless number of polypeptide variants of mammalian sonic hedgehog, yet the specification has not provided sufficient guidance as to which other polypeptides would work as claimed. One of skill in the art appreciates that the many known hedgehog polypeptides provide for a tremendous and disparate

array of developmental controls, determining cell fates in embryonic muscle, lung, and nervous tissues. There is no teaching in the specification as to which of this vast array of proteins, natural or created, could be used in the claimed methods. The prior art is also silent as to which of the proteins, with the exception of sonic hedgehog (see below) could be used to practice the claimed methods. One could only guess at which, if any, could be used; and one of skill in the art would certainly not expect that all could be used.

Applicant argues that, in several studies, each of the hedgehog polypeptides behaved similarly with regard to patched binding and activation of hedgehog signal transduction. This argument has been fully considered but not deemed persuasive. Neither of Applicant's cited references demonstrate that the effects of sonic, Indian, and desert hedgehog are each equivalent to the others. Importantly, in the closest model to that which is being claimed, Engber et al., *Soc. Neurosci. Abs.* 26(1-2)Abs No. 792.14, 2000, report that systemic administration of sonic hedgehog, but not desert hedgehog, improved functional recovery following sciatic nerve crush. Thus, it appears that, in the art of systemic administration of hedgehog for the treatment of neuronal cells, the specificity of the hedgehog polypeptide is critical, in some unknown way, e.g. sonic and desert hedgehog are 80% identical, yet sonic hedgehog is effective in the treatment of sciatic nerve crush whereas desert hedgehog is not.

Further, the claims encompass variants of the disclosed sonic hedgehog polypeptides, yet the specification has not provided sufficient guidance as to how to make such variants. One of skill in the art is left to extensive experimentation wherein amino acids are randomly changed,

deleted, or added to a hedgehog polypeptide, and through trial and error experimentation is left to determine when a polypeptide is obtained that could used to reduce cerebral infarct volume or treat other conditions of neuronal necrosis. Such extensive random trial and error experimentation is considered undue.

Applicant argues that making and testing variants is routine in the art. This argument has been fully considered but not deemed persuasive. Each of the mutants would need to be tested with regard to reducing cerebral infarct volume or to treating other conditions of neuronal necrosis. One highly skilled in the art would certainly not consider such testing of randomly generated mutants to be routine. As evidenced by Engber et al., above, the art regarding systemic administration of hedgehog is unpredictable, and it does not appear that a patched binding assay would be sufficient to identify mutants that would work as claimed because both sonic and desert bind patched but only sonic appears to be effective when systemically administered to treat neuronal cells, absent evidence to the contrary.

Applicant argues that the claims have been limited to variants which possess specific functional attributes. This argument has been fully considered but not deemed persuasive. Simply writing down functional attributes or verbalizing them does not produce polypeptides with those attributes, and nor is it clear that the limited functional attributes Applicant refers to are sufficient to produce the required effect, see above.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

8. Claims 1, 21, 25-28, 39 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No: 5789543.

U.S. Patent No: 5789543 teaches that injury to the nervous system caused by deficit, e.g. ischemia, can be treated with a hedgehog polypeptide, see col 26. U.S. Patent No: 5789543 contemplates treating both the central and peripheral nervous system (col 25, L60-68). U.S. Patent No: 5789543 discloses that the preferred modes of administration are systemic yet particularly points out that other methods might be required for treatment of the central nervous system (col 31, L22-31). Thus the ordinary artisan recognizes that U.S. Patent No: 5789543 teaches that the peripheral nervous, damaged by a deficit, can be treated systemically with a hedgehog polypeptide - ischemia and/or oxygen deprivation being perhaps the best known cause of peripheral nervous system damage resulting from a deficit. Further, the additional treatment methods recited in claims 26-28 are old and established as admitted in the instant specification, e.g. page 9, as also understood by anyone practicing the methods of U.S. Patent No: 5789543.

Applicant argues that U.S. Patent No: 5789543 does not sufficiently link the elements of sonic hedgehog, ischemia, and systemic administration to arrive at the instantly claimed invention. This argument has been fully considered but not deemed persuasive for the reasons above. Applicant's comparison of the instant fact pattern to *In re Meyer* is unpersuasive. The disclosure of Patent No: 5789543 would clearly be interpreted by the ordinary artisan as combining the required elements, as set forth above. Applicant further argues from the stand point of obviousness. Specifically Applicant contends that one of skill in the art would not expect that treatment of the brain could be accomplished through systemic administration of hedgehog proteins. This argument is persuasive and claims now limited to systemic administration for the treatment of stroke and cerebral ischemia have been removed form the rejection.

Conclusion

No claims are allowable.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m. The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

January 10, 2003

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600